(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 535 898 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92308837.1**

(51) Int. Cl.5: **C12M 1/40**

(22) Date of filing: **28.09.92**

(30) Priority: **04.10.91 US 771658**

(43) Date of publication of application:
07.04.93 Bulletin 93/14

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

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(54) Hydrophilic polyurethane membranes for electrochemical glucose sensors.

(57) Homogeneous membranes permeable to oxygen and glucose composed of hydrophilic polyurethanes that are capable of absorbing from 10 to 50% of their dry weight of water. Variations in the composition of the hydrophilic polyurethanes make possible the fabrication of membranes in which the ratios of the diffusion coefficients of oxygen to glucose can be varied over a wide range. These membranes can be used in the fabrication of an electrochemical glucose sensor intended for use in vivo as an aid in the treatment of diabetes mellitus.

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This invention relates to homogeneous membranes composed of hydrophilic polyurethanes that are useful in the fabrication of electrochemical glucose sensors, particularly those intended for in vivo use.

BACKGROUND OF THE INVENTION

At the present time, there are a number of devices commercially available that allow for external monitoring of glucose levels of urine and blood. These devices, however, do not allow for continuous monitoring, and they require a high degree of patient compliance in order to be effective.

Much research has been directed toward the development of a glucose sensor that would function in vivo as an aid, for example, in the treatment of diabetes mellitus. An implantable glucose sensor that would continuously monitor a patient's blood glucose level could serve as a hypo- and hyperglycemia alarm, and would provide physicians with more accurate information in order to develop optimal therapy. In addition, such a sensor would make possible the development of a "closed loop" insulin delivery system in which a pump delivers insulin as needed, rather than on a programmed basis.

Implantable glucose sensors have been developed based on both optical and electrochemical principles. Schultz and Mansouri have disclosed one version of an optical sensor (J.S. Schultz and S. Mansouri, "Optical Fiber Affinity Sensors," Methods in Enzymology, K. Mosbach, Ed., Academic Press, New York, 1988, vol. 137, pp. 349-366). An impediment to the commercial development of an optical sensor of the type disclosed by Schultz and Mansouri has been the difficulty of producing such devices on a commercial basis.

Electrochemical glucose sensors, on the other hand, can be produced using techniques common in the semiconductor industry. The ability to mass produce electrochemical glucose sensors using known commercial techniques gives them a cost advantage over optical sensors. As a consequence, considerable research has been directed toward the development of an in vivo electrochemical glucose sensor. An excellent summary of the issues relating to the development of implantable electrochemical glucose sensors has been published by Turner and Pickup (A.P.F. Turner and J.C. Pickup, "Diabetes Mellitus: Biosensors for Research and Management," Biosensors, 1, 85-115 (1985)).

The most favored configuration to date for an electrochemical glucose sensor involves the use of one or two enzymes to catalyze the reaction between glucose and another molecule in order to generate an electrical signal. Typically, glucose oxidase is used to catalyze the reaction between glucose and oxygen to yield gluconic acid and hydrogen peroxide, as follows:

$$\text{GLUCOSE} + O_2 \xrightarrow[\text{Oxidase}]{\text{Glucose}} \text{GLUCONIC ACID} + H_2O_2$$

$$H_2O_2 \longrightarrow 2H^+ + O_2 + 2e^-$$

The hydrogen peroxide generated may be detected directly or it may be decomposed by a second enzyme, catalase, in which case the sensor will measure oxygen consumption by the reaction involving glucose oxidase.

The presence of an excess of molecular oxygen, relative to molecular glucose, is necessary for the operation of a glucose oxidase based glucose sensor. This presents a problem in the design of such sensors, since the concentration of oxygen in the subcutaneous tissue is much less than that of glucose. As a consequence, oxygen can become a limiting reactant, giving rise to an "oxygen deficit" problem. Some provision should therefore be made to allow operation of the sensor in an environment with an excess of oxygen.

Many attempts have been made to utilize membranes of various types in an effort to ratio the diffusion of oxygen and glucose to the sensing elements of glucose oxidase based glucose sensors to address the "oxygen deficit" problem. The simplest approach to controlling diffusion has been to use a macroporous or a microporous membrane. For example, in U.S. Patent No. 4,759,828, Young et al. disclose the use of a laminated membrane with an outer microporous membrane having a pore size of 10 to 125A to limit the diffusion of glucose molecules. One immediate problem with macroporous or microporous membranes, however, is that the sensing element of the sensor is exposed to the environment of the body and is therefore subject to fouling. Young et al. attempted to obviate this problem by the use of a second inner membrane to exclude passage of fouling substances to the sensing element. This design creates additional

Also, because two membranes are necessary, each membrane must be extremely thin so that measurement times are not unduly long.

Another approach has been to utilize a membrane element that contains discrete hydrophilic and hydrophobic domains. In U.S. Patent No. 4,484,987, Gough discloses a composite membrane in which an immiscible hydrophilic material is physically incorporated in a hydrophobic matrix. The purpose of such a membrane is to achieve a favorable balance between oxygen diffusion through the hydrophobic and hydrophilic matrices and glucose diffusion only through the hydrophilic domains. The effectiveness of such a membrane depends upon the relative amounts of the hydrophilic domains within the hydrophobic matrix. Such membranes are difficult to fabricate reproducibly, particularly on the scale of a glucose sensor meant for implantation within the body. Also, because of the discontinuous nature of the membranes disclosed in Gough '987, physical properties are compromised.

In U.S. Patent No. 4,890,620, Gough discloses a further elaboration of this concept, utilizing a "two-dimensional" sensing electrode. Here the "membrane" element is physically constructed so that oxygen and glucose diffuse to the sensing electrode at right angles to one another, one direction favoring oxygen diffusion and the other favoring glucose diffusion. While a glucose sensor incorporating the diffusion element of Gough '620 may be useful for research purposes, it would be difficult to fabricate on a commercial scale because of its complexity. Additionally, constraints would be placed upon the size and configuration of the sensor in order to allow for diffusion to the sensing electrode from two directions.

Gernet et al. and Shichiri have recognized the above-mentioned difficulties and have utilized a single homogeneous membrane composed of a hydrophobic polyurethane (S. Gernet, et al., "Fabrication and Characterization of a Planar Electrochemical Cell and its Application as a Glucose Sensor," Sensors and Actuators, 18, 59-70 (1989); M. Shichiri, "Glycaemic Control in Pancreatectomized Dogs With a Wearable Artificial Endocrine Pancreas," Diabetologia, 24, 179-184 (1983)). While a homogeneous hydrophobic membrane eliminates many of the difficulties mentioned above, it does not provide an optimum balance between oxygen and glucose transport to an electrochemical glucose sensor, nor is it possible to tailor the properties of the homogeneous hydrophobic polyurethane membrane utilized by Gernet et al. and Shichiri to match the design requirements of electrochemical glucose sensors.

SUMMARY OF THE INVENTION

The primary requirement for an electrochemical glucose sensor intended for in vivo use is that the supply of oxygen in the vicinity of the sensing element not be depleted. This does not mean that an electrochemical glucose sensor membrane need have an extremely high permeability to oxygen. What is needed is a membrane that can moderate the diffusion of oxygen and glucose so that the local concentration of oxygen is not depleted. It is sufficient if the ratio of the diffusion coefficient of oxygen to that of glucose is appropriate to the design of the glucose sensor.

Electrochemical glucose sensors intended for in vivo use must also be rendered biocompatible with the body, and they must be able to function in a hostile environment. The enzyme(s) used in such sensors must be protected from degradation or denaturation. At the same time, the sensing elements of such sensors must be protected from molecules which would foul the sensors or their accuracy will decrease over time.

The membranes of the present invention possess unique attributes that satisfy the above objectives. Their properties can be varied to tailor their glucose and oxygen transport behavior to match the requirements of a particular configuration of an electrochemical glucose sensor. The membranes of the present invention are particularly useful in the construction of electrochemical glucose sensors intended for in vivo use.

The homogeneous membranes of the invention are prepared from biologically acceptable polymers whose hydrophobic/hydrophilic balance can be varied over a wide range to control the ratio of the diffusion coefficient of oxygen to that of glucose, and to match this ratio to the design requirements of electrochemical glucose sensors intended for in vivo use.

The membranes of the invention are fabricated from polymers prepared by the reaction of a diisocyanate, a poly(ethylene oxide), and an aliphatic diol. The polymerization reaction may be carried out in solution or in bulk. The preferred hydrophilic polyurethanes so produced are capable of absorbing from about 10 to about 50% of their weight of water, with those capable of absorbing from about 20% to about 30% of their weight of water being preferred. By appropriate selection of the reaction components, membranes can be made from these preferred polymers that exhibit ratios of the diffusion coefficients of oxygen to glucose of up to about 4000, with ratios of about 2000 to about 4000 being preferred.

Since these polymers do not have to be cross linked in order to develop optimum properties, they are soluble in a variety of solvents and solvent combinations, and thus can be readily fabricated into membranes of various shapes. The membranes of the invention show good adhesion to substrates in an aqueous environment and possess excellent wet-strength. A further advantage of the polymers from which the membranes of the invention are fabricated is that they possess excellent compatibility with the body, a key requirement for an implantable sensor of any type.

It is an objective of the present invention to provide hydrophilic polyurethane membranes for electrochemical glucose sensors to enhance the sensor's biocompatibility and to render the sensor insensitive to changes in the oxygen levels of subcutaneous fluids.

Further and related objects and advantages of the present invention will be apparent from the following description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view of a glucose sensor having sensor elements with a hydrophilic polyurethane membrane of the present invention secured thereover.

FIG. 2 shows in schematic form an implantable portion of a glucose sensor, with the sensing elements covered with a hydrophilic polyurethane membrane of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to the preferred embodiments and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and further modifications in the preferred embodiments, and such further applications of the principles of the invention as illustrated thereby being contemplated as would normally occur to one skilled in the art to which the invention relates.

The present invention provides a novel polyurethane membrane for use in covering or encapsulating a glucose sensor, particularly one intended for in vivo use. It has been discovered that the use of such a membrane provides many advantages including control of the glucose and oxygen reactants to permit accurate analysis, protection of the sensor from the hostile in vivo environment, and biocompatibility.

Referring to the drawings, there is shown in schematic form a glucose sensor 10 of typical construction covered or encapsulated with a membrane fabricated in accordance with the present invention. The specific construction and operation of the sensor 10 do not form a part of the present invention. For example, glucose sensors that utilize glucose oxidase to effect a reaction of glucose and oxygen are known in the art, and are within the skill in the art to fabricate. The present invention depends not on the configuration of the sensor, but rather on the use of a hydrophilic polyurethane membrane to cover or encapsulate the sensor elements. Therefore, only a brief description of an exemplary sensor is given herein. Other sensors for monitoring glucose concentration of diabetics are described, for example, in Shichiri, M., Yamasaki, Y., Nao, K., Sekiya, M., Ueda, N.: "In Vivo Characteristics of Needle-Type Glucose Sensor - Measurements of Subcutaneous Glucose Concentrations in Human Volunteers" - Horm. Metab. Res., Suppl. Ser. 20:17-20, 1988; Bruckel, J., Kerner, W., Zier, H., Steinbach, G., Pfeiffer, E.: "In Vivo Measurement of Subcutaneous Glucose Concentrations with an Enzymatic Glucose Sensor and a Wick Method," Klin. Wochenschr. 67:491-495, 1989; and Pickup, J., Shaw, G., Claremont, D.: "In Vivo Molecular Sensing in Diabetes Mellitus: An Implantable Glucose Sensor with Direct Electron Transfer," Diabetologia. 32:213-217, 1989.

Sensor 10 includes a distal portion 11 in which are located sensor elements 12-14 which are connected through leads 15 to contacts 16. Typical sensing elements would be a counter electrode 12, working electrode 13 and reference electrode 14. Contacts 16 are connected with a suitable monitoring device (not shown), which receives signals and translates this information into a determination of the glucose level detected.

In this type of sensor, glucose oxidase is also provided in the area adjacent the sensor elements, and catalyzes the reaction of glucose and oxygen. This, or a subsequent reaction, is monitored by the sensing elements, and a determination of glucose present in the surrounding subcutaneous tissue may thereby be obtained.

In one design, the sensor 10 includes a substrate material 17 comprising an electrical insulator. This substrate is preferably flexible to facilitate patient comfort. The counter, working and reference electrodes 12-14 are positioned on the substrate and isolated from one another by an insulation layer 18 patterned to

working electrode and all three sensor/electrodes are then covered with a membrane 20 of the present invention.

The distal portion of the sensor is implanted subcutaneously into the body, and the proximal portion including contacts 16 remains external of the body. In accordance with the present invention, the implanted sensor elements 12-14 are covered with a membrane 20 of the present invention, which controls the rate of diffusion of glucose and oxygen from the surrounding body tissue to the area of the sensor elements. Membrane 20 may fully encapsulate the entire distal portion of the sensor or may simply be layered over the sensor elements. The latter approach may be preferable from the standpoint of ease of fabrication.

The membrane of the invention is formed from a hydrophilic polyurethane. Polyurethane is a thermoplastic polymer produced by the condensation reaction of a polyisocyanate and a hydroxyl-containing material. The membrane is characterized by absorbing from about 10% to about 50%, and preferably from about 20% to about 30%, of its weight in water. Also, the membrane's diffusion coefficient for oxygen should be up to about 4000 times the membrane's diffusion coefficient for glucose, and more preferably between about 2000 and about 4000. Within these preferred ranges, a person skilled in the art can synthesize a variety of suitable polyurethane compositions and readily determine the usefulness of such in the formation of membranes of the present invention.

The preferred membranes of the invention were prepared by the reaction of a diisocyanate with a poly-(ethylene oxide) and an aliphatic diol. Preferred diisocyanates include aliphatic diisocyanates containing from 4 to 8 methylene units. In particular, hexamethylene-1,6-diisocyanate has been the most preferred aliphatic diisocyanate in work completed to date. Diisocyanates containing cycloaliphatic moities, such as isophorone diisocyanate and dicyclohexylmethane-4,4'-diisocyanate, may also be used with the latter being the most preferred cycloaliphatic diisocyanate. Aromatic diisocyanates may also be used, but they are less suitable for a medical application because of their extreme toxicity.

The diol component of the polymerization mixture includes a poly(ethylene oxide) and an aliphatic diol. The poly(ethylene oxide) may have an average molecular weight of from 200 to 3000 with a preferred molecular weight range of 600 to 1500, and preferably constitutes about 10 to 50 mole % of the total diol component of the polymerization mixture. Suitable aliphatic diols include ethylene glycol, diethylene glycol, 1,2-propanediol, 1,3-propanediol, and 1,4-butanediol. As will be appreciated by those skilled in the art, other aliphatic diols may be used. These preferred aliphatic diols are chosen for reasons of cost, commercial availability, solubility, reactivity, or ease of purification The aliphatic diol preferably constitutes about 50 to 90 mole % of the total diol component of the polymerization mixture.

Polymerization was carried out using equimolar quantities of total diol and the diisocyanate. Since the poly(ethylene oxide) is hydrophilic, and the aliphatic diol is hydrophobic, variation in the molar ratio of the two will allow for the preparation of polymers with varying hydrophilic/hydrophobic balances. By a suitable choice of the molar amount and the molecular weight of the poly(ethylene oxide) and the molar amount and specific aliphatic diol, polymers can be prepared that vary from being slightly hydrophilic to very hydrophilic and which can be tailored to have ratios of the diffusion coefficient of oxygen to that of glucose of up to 4000, with ratios of about 2000 to about 4000 being preferred. Polymers having ratios of the diffusion coefficient of oxygen to glucose greater than about 4000 may be too impermeable to glucose and provide too slow a response time. Those membranes with ratios less than about 2000 may result in oxygen deficiency for electrochemical glucose oxidase based sensors.

Polymerization may be carried out in bulk or in a solvent system. Although polymerization may be carried out without a catalyst, the addition of a suitable organometallic compound such as dibutylin bis(2-ethylhexanoate) has been preferred. Bulk polymerization was typically carried out at an initial temperature of about 25°C, typically 50°C, in order to insure adequate mixing of the reactants. Upon mixing of the reactants, an exotherm was typically observed, with the temperature rising to approximately 100°C. After this initial exotherm, the reaction flask was heated at from 75 to 125°C, with 90 to 100°C being a preferred temperature range. Heating was usually carried out for one to two hours. Solution polymerizations were carried out in a similar manner. Suitable polymerization solvents have been dimethylformamide, dimethyl sulfoxide, dimethylacetamide, halogenated solvents such as 1,2,3-trichloropropane, and ketones such as 4-methyl-2-pentanone. Dimethylformamide has been a preferred solvent. When polymerization was carried out in a solvent, heating of the reaction mixture was typically carried out for three to four hours.

Polymers prepared by bulk polymerization were dissolved in dimethylformamide and precipitated from water. Polymers prepared in solvents that are not miscible with water were isolated by vacuum stripping of the solvent. These polymers were then dissolved in dimethylformamide and precipitated from water. After thoroughly washing with water, polymers were dried in vacuo at 50° C to constant weight.

16. The device of claim 15 in which said composition absorbs about 20% to about 30% of its weight in water.

17. The device of claim 13 in which said membrane is formed from a polymer comprising the reaction product of:

a diisocyanate selected from hexamethylene-1,6-diisocyanate; dicyclohexylmethane 4,4'-diisocyanate; and isophorone diisocyanate, and constituting about 50 mole % of the reaction mixture;

a poly(ethylene oxide) having an average molecular weight of about 600 to about 1500, and constituting from about 10 to about 50 mole % of the total diol content of the reaction mixture; and

an aliphatic diol selected from ethylene glycol; diethylene glycol; 1,2-propanediol; 1,3-propanediol; and 1,4-butanediol, and constituting about 50 to about 90 mole % of the total diol content of the reaction mixture.

18. The device of claim 17 in which the aliphatic diol is diethylene glycol.

19. The device of claim 17 in which the poly(ethylene oxide) has an average molecular weight of about 600.

20. The device of claim 18 in which the diisocyanate is hexamethylene-1,6-diisocyanate.

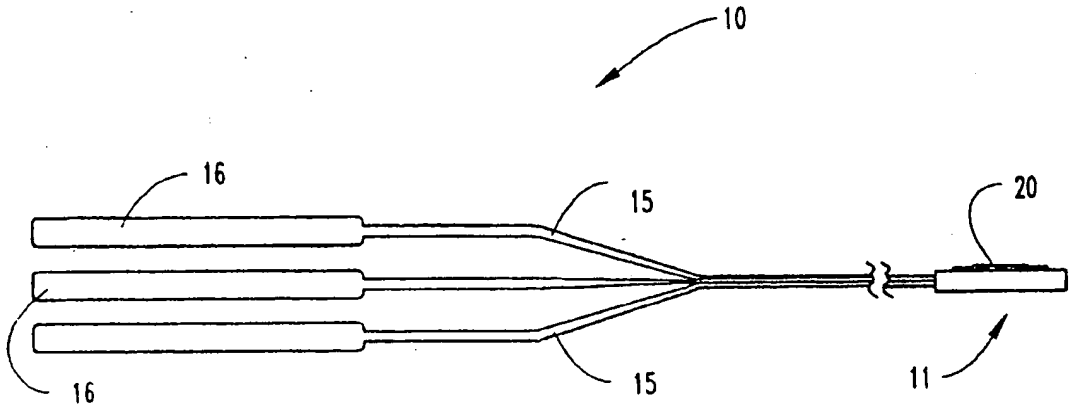

Fig.1

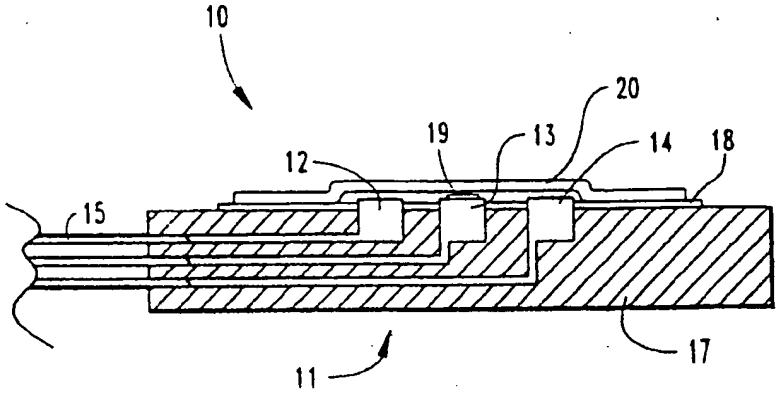

Fig.2

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 30 8837

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 379 149 (THE DOW CHEMICAL COMPANY) ---		C12M1/40
A	WO-A-9 013 021 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) ---		
D,A	US-A-4 759 828 (CHUNG C. YOUNG ET AL.) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C12Q

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20 JANUARY 1993	CARTAGENA ABELLA P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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